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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER

WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
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1632

25

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/087,513

Applicant(s)

KANEKO ET AL.

Examiner

Michael C. Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14, 15, 19 and 21-36 is/are pending in the application.
- 4a) Of the above claim(s) is/are withdrawn from consideration.
- 5) ☐ Claim(s) is/are allowed.
- 6) ☒ Claim(s) 14, 15, 19, 21-36 is/are rejected.
- 7) ☐ Claim(s) is/are objected to.
- 8) ☐ Claim(s) are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s).
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6) ☐ Other:

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DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Specification

The objection to the specification has been withdrawn because the phrase "15, incorporated by reference herein in its entirety" has been deleted.

Claim Rejections - 35 USC § 112

I. Claims 21, 24, 26 and 27 remain rejected and claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The phrase "deletion of amino acids 297-329 in said variable loop" remains new matter (claims 21, 24, 26, 27, 30 and 34). The specification does not give any indication that the deletion is an amino acid deletion and not a nucleic acid sequence deletion. Nor is it readily apparent to one of skill in the art at the time of filing that the deletion is of amino acids. Applicants argue the variable loop of HIV was well known and as a result one of skill in the art would know the description of the 297-329 deletion referred to an amino acid sequence. Applicants supply Back et al. (1993), which describes the

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gp41 coding region and the hypervariable region. Applicants' arguments are not persuasive. The specification teaches the deletion was made using PCR products, which are nucleic acids (pg 26, line 16). Thus, it appears as though the deletion is of nucleic acids. Back et al. does not teach the deletion claimed was amino acids and not nucleic acids. The mere reference to the V3 loop of HIV-1 III B by Back et al. does not support applicants' position. It is not readily apparent from Back et al. that the deletion described in the specification must be amino acids 297-329. Nor is it readily apparent that the deletion described in the specification refers to the HIV isolated described by Back et al. Applicants have not provided adequate evidence that the deletion of 297-329 in the V3 loop must refer to amino acids and cannot refer to nucleic acids.

Therefore, it is not readily apparent that the deletion refers to amino acids.

The specification as originally filed does not provide support for the phrase "introducing into a vector DNA or liposome a nucleic acid encoding an envelope..." on pg 1, lines 6-10, pg 21, line 22 or pg 22, line 14 (claims 28-36).

The specification as originally filed does not provide support for APCs with adjuvant on pg 1, lines 6-10, pg 21, line 22 or pg 22, line 14 (claims 29 and 33).

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II. Claims 14, 15, 19 and 21-27 remain rejected and claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The claims require DNA encoding an envelope glycoprotein of HIV having a deletion of the third variable loop. The only DNA disclosed in the specification having a deletion of the V3 loop as claimed are vv- Δ V3 (pg 26, line 16), 1 Δ V3, 7 Δ V3 and 8 Δ V3 (pg 34). The specification does not provide adequate written description for one of skill to make the DNA disclosed in the specification having a deletion of the V3 loop.

The specification does not provide adequate written description for vv- Δ V3. Kmiecik et al. (June 1, 1998, J. Immunol., Vol. 160, pg 5676-5683) teaches vv- Δ V3 was made using "the Δ 297-329 deletion" taught by Wyatt (Dec. 1992, J. Virology, Vol. 66, pg 6997-7004). The Δ 297-329 deletion of Wyatt was a deletion spanning the V3 loop, wherein Gly-Ala-Gly was inserted in place of the loop. Wyatt also taught the strain of HIV used to make the Δ 297-329 deletion was HXBc2 (pg 6998, col. 1, 2nd para.). The specification does not teach the Δ 297-329 deletion had Gly-Ala-Gly inserted in its place. The specification does not teach the starting material was HXBc2. In fact, the specification teaches the strain was HIVIIIB. Nor does the specification reference Wyatt. The specification does not teach which nucleic acids are 297-329 and such nucleotides cannot be determined from the art. Are the numbers describing the V3 loop or the HIV IIIB genome? Did nucleotides 297-329 have an art accepted meaning at the

time the invention was made? As such, the specification does not provide adequate written description for one of skill to make vv- Δ V3.

Applicants argue the variable loop of HIV was well known and as a result one of skill in the art would have known the deletion of 297-329 referred to an amino acid sequence. Applicants supply Back et al. (1993) which described the gp41 coding region and the hypervariable region. Applicants' arguments are not persuasive. The specification teaches the deletion was made using PCR products (pg 26, line 16). Thus, the specification appears to be describing a deletion of nucleic acids 297-329 because PCR products are nucleic acids. Back et al. does not teach the deletion described in the specification or claimed was amino acids and not nucleic acids. The mere reference to the gp41 coding region, the hypervariable region and the V3 loop of HIV-1 III B by Back et al. does not support applicants' position. It is not readily apparent from Back et al. that the deletion described in the specification must be amino acids 297-329. Nor is it readily apparent that the deletion described in the specification refers to the HIV isolated described by Back et al. Applicants have not provided adequate evidence that the deletion of 297-329 in the V3 loop must refer to amino acids and cannot refer to nucleic acids. Therefore, it is not readily apparent that the deletion of 297-329 described in the specification refers to amino acids.

Applicants argue it was known that the pSVIII-env plasmid with the Δ 297-329 deletion had an insertion of Gly-Ala-Gly as supported by Wyatt et al. (1992). Applicants' argument is not persuasive. The specification teaches the starting material was HIV IIIB (pg 26, line 12), not HXBc2 as described by Wyatt. One of skill would not have known

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the $\Delta 297-329$ mutant described on pg 26, line 16, had an insertion of three amino acids as described by Wyatt based on the description originally filed. Nowhere does the specification as originally filed imply that three amino acids were inserted. Nor does the specification imply that the $\Delta 297-329$ is limited to the vector described by Wyatt et al. in which three amino acids are inserted into the deletion. One of skill in the art at the time of filing would not have reasonably concluded that the $\Delta 297-329$ mutant described on pg 26, line 16, was limited to the $\Delta 297-329$ mutant described by Wyatt et al. One of skill in the art at the time of filing would not have reasonably concluded that vv- $\Delta V3$ described in the specification was limited to the $\Delta 297-329$ mutant described by Wyatt et al.

The specification does not provide adequate written description for the 1 $\Delta V3$, 7 $\Delta V3$ and 8 $\Delta V3$ mutants. The specification discloses the 1 $\Delta V3$, 7 $\Delta V3$ and 8 $\Delta V3$ mutants in Example 14 (page 34, Fig. 1) but does not teach how to make such mutants, how the mutants differ from each other, how the mutants differ from the vv- $\Delta V3$ mutant with the $\Delta 297-329$ deletion (page 26) or the structural elements of the mutants. The specification discloses the WTP-2, WTP-5 and WTP-8 (page 35, line 3; page 36, line 16; Fig. 1), but it is unclear how the envelope gene in these vectors differs from each other or from the V3 mutants or whether these vectors are considered "modified".

Applicants' arguments refer to the "WP and vv $\Delta V3$ mutants" (pg 6, line 5), which is unclear because the rejection is based on how to make 1 $\Delta V3$, 7 $\Delta V3$ and 8 $\Delta V3$ mutants and because WP is not a vector described in the specification. Applicants argue, "[t]he constructs with the wild type V3 clone from clone pIIIB to yield pSC-WTP

(see page 27, lines 10-13)." Applicants' argument cannot be determined because the sentence is incomplete. Applicants argue pg 27, lines 12-13, describe "the vv-ΔV3 and vvWTP were generated using the wild type (WT) and V3 mutant plasmids discussed above." Applicants' argument cannot be determined because it is unclear how "vv-ΔV3 and vvWTP" correlate to 1ΔV3, 7ΔV3 and 8ΔV3 mutants and because pg 27, lines 10-13, do not describe making 1ΔV3, 7ΔV3 or 8ΔV3 mutants, or how pSC-ΔV3 and pSC-WTP were used to generate vv-ΔV3. Example 14 (pg 34, Fig. 1) does not refer to any vectors described on pg 27. The structure of the 1ΔV3, 7ΔV3 and 8ΔV3 mutants cannot be determined because the backbone vector and the mutations made to the backbone vector required to create 1ΔV3, 7ΔV3 and 8ΔV3 mutants are not described in the specification, specifically in Example 14 (pg 34-35) taken with pg 27, lines 10-13.

Claims 14, 15, require the product made is a vaccine against HIV. Claims 19 require the product is a vaccine that induces cellular immunity against HIV. Claim 28 requires stimulating a CTL response against HIV. Claims 32-36 require stimulating a CTL response in a patient. The only disclosed purpose for vaccinating against HIV, inducing cellular immunity against HIV or stimulating a CTL response against HIV is to treat or prevent HIV infection (pg 1, line 12; pg 23, line 9). The specification does not provide adequate written description for any DNA encoding an envelope glycoprotein of HIV with a deletion in V3 capable of treating or preventing HIV, specifically capable of inducing a cellular immune response against HIV that is therapeutic or prophylactic.

The specification does not provide adequate written description for DNA encoding an HIV envelope glycoprotein having a deletion in the V3 loop or a cell

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expressing such an envelope glycoprotein that is capable for being used to treat or prevent HIV, specifically to induce a therapeutic or prophylactic cellular immune response against HIV. The specification does not teach obtaining a cellular immune response that is directed toward HIV or obtaining a therapeutic or prophylactic effect against HIV using the DNA or cells as claimed. The art at the time of filing did not teach how to obtain such an effect using DNA encoding an HIV envelope protein having a deletion in the V 3 loop. Without such guidance, the specification does not provide adequate written description for the structure of any DNA encoding an envelope glycoprotein of HIV with a deletion in V3 having the function of treating or preventing HIV.

Applicants provide Rowland-Jones et al. as support for the importance of HIV-specific CTL in controlling viral levels during infection. Applicants' argument is not persuasive because Rowland-Jones et al. (1999) was not available to one of skill in the art at the time of filing. Applicants provide Kiska et al. as support for $\Delta V3$ mutants that produce a CTL response. Applicants' argument is not persuasive because Kiska et al. (2002) was not available to one of skill in the art at the time of filing. In addition, it is not readily apparent that the $\Delta V3$ mutants described by Kiska et al. (pg 4223, col. 2, 1st full para.) correlate to the $\Delta V3$ mutants described in the specification. The means by which $\Delta V3$ mutants described by Kiska et al. induced a CTL response against gp160 *in vivo* is not described in the specification. Applicants reference to pg 13, col. 1, of Kiska et al. (pg 7, line 11, of response) does not exist; Kiszka et al. is pg 4222-4232. The citation cannot be determined. Overall, applicants have not provided adequate post-filing

evidence indicating the specification as originally filed described how to make a composition capable of treating or preventing HIV infection.

Applicants also refer to Kmiecik et al. (pg 7, line 18, of response) which was not available at the time of filing (May 29, 1998).

III. Claims 14, 15, 19 and 21-27 remain rejected and claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

The claims require DNA encoding an envelope glycoprotein of HIV having a deletion of the third variable loop. The only DNA disclosed in the specification having a deletion of the V3 loop as claimed are vv- V3 (pg 26), 1 V3, 7 V3 and 8 V3 (pg 34). The specification does not enable one of skill to make the Δ V3 mutants disclosed in the specification.

The specification does not enable one of skill to make vv- V3. Kmiecik et al. (June 1, 1998, J. Immunol., Vol. 160, pg 5676-5683) teaches vv- V3 was made using "the Δ 297-329 deletion" taught by Wyatt (Dec. 1992, J. Virology, Vol. 66, pg 6997-7004). The Δ 297-329 deletion of Wyatt was a deletion spanning the V3 loop, wherein Gly-Ala-Gly was inserted in place of the loop. Wyatt also taught the strain of HIV used to make the Δ 297-329 deletion was HXBc2 (pg 6998, col. 1, 2nd para.). The specification does not teach the Δ 297-329 deletion had Gly-Ala-Gly inserted in its place.

The specification does not teach the starting material was HXBc2. In fact, the specification teaches the strain was HIVIIB. Nor does the specification reference Wyatt. The specification does not teach which nucleic acids are 297-329 and such nucleotides cannot be determined from the art. Are the numbers describing the V3 loop or the HIV IIB genome? Did nucleotides 297-329 have an art accepted meaning at the time the invention was made? As such, the specification does not enable one of skill to make vv- V3.

The specification does not enable one of skill to make 1 V3, 7 V3 or 8 V3. The specification discloses the 1 V3, 7 V3 and 8 V3 mutants in Example 14 (page 34, Fig. 1) but does not teach how to make such mutants, how the mutants differ from each other, how the mutants differ from the vv- V3 mutant with the Δ 297-329 deletion (page 26) or the structural elements of the mutants. The specification discloses the WTP-2, WTP-5 and WTP-8 (page 35, line 3; page 36, line 16; Fig. 1), but it is unclear how the envelope gene in these vectors differs from each other or from the V3 mutants or whether these vectors are considered "modified".

Claims 14, 15, 21, 22 and 26 require the product made is a vaccine against HIV. Claims 19, 23-25 and 27 require the product induces cellular immunity against HIV. The only disclosed purpose for vaccinating against HIV or inducing cellular immunity against HIV is to treat or prevent HIV infection (pg 1, line 12; pg 23, line 9). The specification does not enable one of skill to use DNA encoding Δ V3 mutants to treat or prevent HIV.

At the time of filing, it was unpredictable whether a nucleic acid construct would have a therapeutic or prophylactic effect against HIV. Ross of record (September 1996, Human Gene Therapy, Vol. 7, pages 1781-1790) states a major technical impediment to gene transfer is the lack of ideal gene delivery systems including vectors, promoters and modes of delivery (page 1782, column 2, first full paragraph). These technical parameters are required to obtain efficient delivery and sustained expression of the gene (Verma of record, Sept. 18, 1997, Nature, Vol. 389, page 239-242; see page 239, 3rd column, line 10). The difficulties in sustaining expression of a gene cause unpredictability in obtaining a therapeutic or prophylactic effect in a patient (Ross, page 1789, column 1, first paragraph). Therefore, the parameters required to obtain a therapeutic effect using DNA were unpredictable at the time of filing.

Regarding vaccines, it was unpredictable how to obtain a therapeutic effect against a virus using a single antigenic stimulus as a vaccine. Haynes of record (1993, Science, Vol. 260, pages 1279-1286) teaches the classic approach to vaccine development involves exposing cells of the immune system to the proper antigenic stimulus which stimulates a beneficial immune response. The prior art presents few examples where a single antigenic stimulus, such as a small limited peptide or a whole protein is found to engender a therapeutic or protective immune response. The successful art-recognized immunogens used as vaccines are derived from whole killed or live attenuated pathogens, comprised of complex antigenic mixtures or comprised of inactivated toxins. Many of these successes were achieved with a certain degree of luck, influenced by some particular peculiarity or aspect of a given pathogenic agent.

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Therefore, it was unpredictable how to obtain a therapeutic effect against a virus using a single antigen.

Specifically regarding HIV vaccines, Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9; see page 527, last paragraph through all of page 528) teaches that attempts to develop a vaccine against HIV have been unsuccessful. In fact, HIV infection has defied the creation of an effective vaccine or immunotherapeutic. Overall, a lack of understanding about cellular immunity against HIV, the sequence variability of HIV and the rapid replication of HIV, as disclosed by Bangham of record contribute the ineffectiveness of vaccines against HIV (Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of column 1). It is not known what renders an antigen capable of stimulating beneficial or protective CTL responses to HIV.

Therefore, the art at the time of filing did not teach that the envelope glycoprotein of HIV could be used to induce a therapeutic cellular immune response against HIV. Thus, the parameters required to obtain a therapeutic cellular immune response against HIV was unpredictable at the time of filing.

The specification does not enable one of skill in the art to use DNA encoding $\Delta V3$ mutants or a cell expressing $\Delta V3$ mutants for treatment or prevention HIV. The specification does not teach obtaining a cellular immune response that is directed toward HIV, obtaining a therapeutic or prophylactic immune response against HIV using DNA encoding $\Delta V3$ mutants, specifically obtaining a therapeutic or prophylactic cellular immune response against HIV using DNA encoding $\Delta V3$ mutants. The art at the time of filing did not teach how to obtain such an effect using DNA encoding $\Delta V3$ mutants.

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Without such guidance, the specification does not enable one of skill in the art to use DNA encoding $\Delta V3$ mutants to treat or prevent HIV.

Applicants' arguments regarding the enablement issues described above are addressed in the response to the arguments regarding the written description rejection.

The specification provides CTL and antibody-dependent cell-mediated cytotoxicity data *in vitro* (page 35-38), but does not provide any examples of inducing cellular immunity against HIV *in vivo*. Nor does the specification provide adequate correlative evidence between *in vitro* data and *in vivo* results such that a therapeutic cellular immune response against HIV could be obtained *in vivo*.

The state of the art at the time of filing was that CTL assays *in vitro* produce variable results depending on the target cells used, the effector to target ratio used, and the incubation time (Lancki of record, 1992, Biotherapy, Vol. 5, pages 71-81; see page 72, column 1, line 1) CTL assays combine PBL and target cells that are artificially "loaded" with antigen. The amount of antigen required on the target cell surface to induce a CTL response depends upon the immunostimulatory epitope of the antigen, the type of immune response and the strength of the immune response desired. Moreover, CTL assays do not account for the complex interaction of the immune response and cytokine regulation that occurs *in vivo*. For example, Bachmann of record reviews the use of the cellular immune response both *in vivo* and *in vitro* in viral assay systems (1994, Current Op. Immunol. Vol. 6, pages 320-326). A comparison of sensitivities shows that radioactive CTL assays are more sensitive than *in vivo* assays, but that results of secondary *in vitro* stimulation need to be verified by *in vivo* assay. On

page 323, Bachmann states one should be very cautious not to 'over-interpret' results obtained by a cytolytic assay where cells are stimulated *in vitro* because the results may be biologically irrelevant without *in vivo* confirmation. Therefore, it was unpredictable at the time of filing whether a CTL response obtained *in vitro* could be obtained *in vivo* or that a cellular immune response obtained *in vivo* equivalent to the cellular immune response obtained *in vitro* will have any biological relevance.

The *in vitro* CTL and ADCC assays disclosed in the instant application require PBMC isolated from an HIV patient and autologous B-LCL or Jurkat cells transfected with the vectors of the invention as target cells which do not correlate to cells or nucleic acids used to treat viral infection *in vivo*. The specification does not teach the strain of HIV in the patients used to make the PBMC *in vitro*, the level of antigen expression on the surface of target cells *in vitro*, the level of expression required *in vivo*, or how the immune response obtained *in vitro* correlates to response expected *in vivo*. It is not clear that the ratios of target to effector ratio used *in vitro* correlates to the ratio of transfected cells to effector cells that would occur *in vivo*. In addition, applicants activated the PBMC with antibodies which is an artificial means used to increase the activity of the cytotoxic cells and does not correlate to conditions found in the HIV patients because patients PBMCs are not stimulated with anti-CD3 antibodies. In addition, the specification does not teach that the level of cellular immunity *in vitro* would have any therapeutic benefit in a patient. Given the state of the art regarding the lack of correlation between *in vitro* and *in vivo* cytotoxicity taken with the guidance provided in the specification, it would have required one of skill undue experimentation to determine

the parameters required to obtain an cellular immune response *in vivo* that has a therapeutic or prophylactic effect.

Claims 14, 15, 19, 21, 23, 24, 28-30, 32-34 and 36 encompass modifying the envelope glycoprotein of any strain of HIV. The state of the art at the time of filing was such that the V3 region of HIV varied between HIV strains and mutated frequently (page 1, line 15; page 2, line 13; page 3, line 3). The specification only teaches modifying the V3 loop of the HIV-IIIB envelope glycoprotein (page 26, line 12). The specification does not teach how to modify the V3 loop of the envelope glycoprotein of any other strain of HIV or correlate the V3 loop of HIV-IIIB to other strains of HIV such that similar modifications could be made or that a therapeutic cellular immune response could be induced against the glycoprotein.

Applicants demonstrate different modifications of HIV-IIIB cause different effects (e.g. 1 V3, 7 V3 or 8 V3 mutants induce different immune responses, Fig. 1). Therefore, the specification does not enable one of skill to determine how to modify the V3 loop of any HIV envelope glycoprotein such that a therapeutic cellular immune response against HIV is obtained.

Overall, the specification does not provide adequate guidance regarding how to induce a therapeutic cellular immune response against HIV *in vivo*. Given the state of the art taken with the guidance provided in the specification, it would require one of skill undue experimentation to determine how to use DNA encoding Δ V3 mutants to induce a therapeutic or prophylactic cellular immune response against HIV.

IV. Claims 21, 24, 26 and 27 remain rejected and claims 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

It is unclear from the specification that the deletion of the V3 loop is of amino acids 297-329 as claimed and not of nucleotides 297-329 in the DNA. Applicants have not addressed this rejection.

Claims 28-36 are indefinite because the phrase "introducing into a vector DNA or liposome a nucleic acid encoding an envelope..." is grammatically unclear. A nucleic acid does not encode anything because it is a molecule; a nucleic acid sequence encodes an envelope protein. The metes and bounds of how a nucleic acid is "introduced" into "vector DNA" or a "liposome" are unclear. Use of the phrase "vector DNA" is unclear because it does not have an art established meaning and cannot be found in the specification. Putting a nucleic acid into a vector is a completely different process than putting a nucleic acid into a liposome carrier; therefore, combining the two concepts into one step is confusing.

Claims 29 and 33 are indefinite because it is unclear whether the "adjuvant" in claim 29 is the adjuvant of claim 28 or a different adjuvant.

Claims 14, 15, 21, 22 and 26 appear to be free of the prior art of record because the prior art of record did not teach or suggest combining DNA encoding a Δ V3 mutant with adjuvant. Claims 19, 23-25 and 27 appear to be free of the prior art of record

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because the prior art of record did not teach or suggest combining cells expressing DNA encoding a $\Delta V3$ mutant with adjuvant.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

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If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

A handwritten signature in black ink, appearing to read 'Michael C. Wilson', with a stylized, cursive script.

**MICHAEL WILSON
PRIMARY EXAMINER**